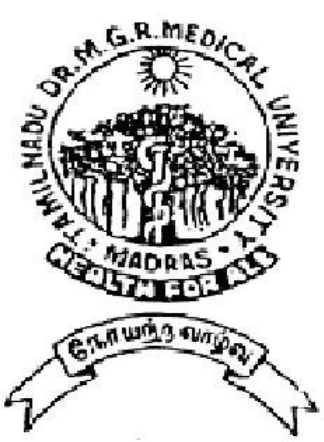
A DISSERTATION ON

CLINICO - EPIDEMIOLOGICAL PROFILE, CD4 CORRELATION AND OUTCOME OF PAEDIATRIC HIV

M.D (BRANCH VII)

PAEDIATRIC MEDICINE

MARCH 2009



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CERTIFICATE

This is to certify that the dissertation titled **"Clinico epidemiological profile, CD4 correlation and outcome of paediatric HIV"** submitted by **Dr.M.Vaideeswaran** to the Faculty of pediatrics,The Tamilnadu M.G.R.Medical University,Chennai in partial fulfillment of the requirement for the award of M.D.Degree (Pediatrics) is a bonafide research work carried out by him under our direct supervision and guidance.

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DECLARATION

I **Dr.M.Vaideeswaran**, solemnly declare that the dissertation titled "**Clinico epidemiological profile, CD4 correlation and outcome of paediatric HIV"** has been prepared by me.

This is submitted to the **Tamilnadu Dr.M.G.R.Medical University**, Chennai in partial fulfillment of the rules and regulations for the M.D.Degree Examination in Paediatrics.

Place: Madurai

Date: **Dr.M. VAIDEESWARAN**

ACKNOWLEDGEMENT

I am greatly indebted to my teacher, **Prof. Dr.P.Amutha Rajeswari**, Professor and Head of the Department of Pediatrics, for her supervision, guidance and encouragement while undertaking this study.

I would like to thank **Prof. Dr.M.L.Vasanthakumari** who guided me to a great extent for her valuable suggestions and guidance.

I am also extremely grateful to my unit chief **Prof. Dr.Chitra Ayyappan**, for the guidance which has helped me a lot in completing the work successfully.

I also would like to thank **Prof. Dr. G. Mathevan**, for his guidance and suggestions.

I also thank all the members of the Dissertation committee for their valuable suggestions. I gratefully acknowledge the help and guidance received from **Asst.Prof. Dr. M. Kulandaivel, Asst. Prof. Dr.M. Balasubramanian, Asst.Prof. Dr. Nataraja rathinam** at every stage of this study.

I am indebted to **Prof. Dr.Uma**, Head of the Department, Microbiology for her support.

I thank the **Dean** and the **members of the Ethical committee**, Government Rajaji hospital, Madurai for permitting me to perform this study.

I am grateful to **Prof. Dr. Thirumalai kolundu subramaniam,** Retired

Professor of Medicine, GRH, Madurai, for his valuable suggestions and guidance.

I would like to thank **Mr. R. Balasubramanian, Statistician**, Council of Medical Research and Entomology who helped me a lot.

I also express my gratitude to all my fellow **postgraduates** for their kind cooperation in carrying out this study and for their critical analysis.

Last but not the least, I am indebted to all the **children enrolled in this study and their parents** without whose cooperation, this study would not have been possible.

CONTENTS

INTRODUCTION

Acquired immunodeficiency syndrome is caused by infection with human immunodeficiency virus type 1 and rarely type 2. The HIV pandemic has spread word wide since 1981.The first paediatric case of AIDS was reported to the centre for disease control and prevention in November 1982. Since then HIV infection in children represents a major setback to child health all over the world

Statement of problem and need of the study:

India harbours world's second highest number of HIV infected people (1). HIV infection is increasingly becoming a prominent cause of childhood morbidity and mortality in India. Presently, 2, 02,000 children are living with HIV/AIDS in India. 50% of these die within 2 years, constituting about 18% of 3.1 million AIDS deaths every year (2). Despite the magnitude of the problem, there is paucity of data on various issues in paediatric HIV infection from India. In spite of that it is now well known that the epidemiological and clinical features differ greatly from country to country. The epidemiological features depend upon the social and cultural practices of those people which may again vary from region to region. Opportunistic infections (OIs) are an important cause of morbidity and mortality in children infected with HIV. The clinical features and opportunistic infections of HIV infection may depend on the

organisms and parasites endemic in that country. However, few data are available regarding the overall prevalence, incidence and immunologic correlates associated with these diseases in the paediatric HIV population. We undertook this study to identify the epidemiological, clinical background and its correlation with CD4 values and the outcome of these children.

NATURAL HISTORY:

Perinatal transmission is the main mode of acquisition of HIV infection in children and also via blood products and rarely homosexual or heterosexual in adolescents. A bimodal distribution of disease progression is seen in vertically transmitted HIV infection in children. Early onset of symptoms at younger than 12 months of age with rapidly progressive disease and high mortality is observed in 10-25 percent of infected infants. The majority of children with vertical transmission appear to have later onset symptoms and a better prognosis, with median time to development of AIDS of more than 5 years and survival of 6-9 years. Early age of disease onset is a marker of poor prognosis.

REVIEW OF LITERATURE

Most studies about paediatric HIV infection came from the developed countries. No such large scale information is available in India. HIV infection being a global emergency and spreading like a pandemic, the number of children affected with HIV infection is rapidly increasing. Most of the studies related to clinical profile of HIV came in the pre –ART era.

Highly active anti-retroviral therapy (HAART) has changed the face of HIV/AIDS by leading to a dramatic decrease in HIV-related morbidity and mortality among those with access to therapy (3). Until recently, HAART was not accessible to a vast majority of the 5.1 million Indians living with HIV in India (4) primarily due to its high cost. There was a significant decrease in the number of incident opportunistic infections, especially tuberculosis, in patients on HAART.

The advent of potent antiretroviral drugs has enabled transformation of human immunodeficiency virus (HIV) infection from a fatal to a chronic disease in developed countries (5). However supportive care, appropriate prophylaxis and management of infections are equally important. They are, in fact, the mainstay of therapy in countries such as ours where antiretroviral therapy is ill affordable by most patients (6). The introduction of HAART become more available, descriptions of treated disease will include side effects and toxicities of therapy. In addition, Indian children are also

afflicted by wasting, malnutrition, and chronic diarrhoeal disease. Appropriate immunizations, prophylaxis with cotrimoxazole, and preventative measures such as boiling water must be taken in order to avoid morbidity and mortality in children. Little is known about the natural history of HIV disease in Indian children, and further research is needed.

The proposed study evaluates the clinical profile including opportunistic infections in relation to CD4 and determines the response to antiretroviral therapy.

Initial evaluation in HIV infected children includes detailed history to ascertain the mode of transmission, symptoms related to HIV and HIV status of the family members. The socioeconomic status and level of disease awareness in the caretakers should also be enquired into. A detailed physical examination including anthropometry, pulse oximetry, fundoscopy and neurodevelopment assessment should be carried out.

Subsequently if feasible, the immune status and viral burden should be determined by estimation of CD4 counts and HIV RNA levels. Other laboratory tests include a complete hemogram including platelet count, liver and renal function tests, and X ray film of the chest, tuberculin test, stool examination, urine analysis and ECG. Immunoglobulin levels, echocardiogram, computerized tomography (CT) of the chest and plain head CT may be requested if indicated.

After clinical and immune categorization of the illness, treatment details are planned and discussed with the caretakers.

PRE ART EVALUATION AND FOLLOW UP

S.No.	Evaluation	Interval
1.	Complete history and physical examination	3 months
2.	Review of systems	3 months
3.	Development examination	
	< 1 year age	3 months
	1-3 years	6 months
	> 3 years	Annually
4.	Chest radiography	Annually
5.	Laboratory tests	
	Complete blood counts	3 months
	CD4 / CD8	3 months
	LFT	3 months
	RFT	Baseline and as indicated
	Urine analysis	Annually
6.	Mantoux test	Annually
7.	Referrals	
	Ophthalmology	Annually
	Cardiology	If indicated

Antiretroviral therapy:

Antiretrovirals can be classified as nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). As many as 13 antiretroviral agents are currently FDA approved for treatment of HIV infection (5). NRTIs were the first drugs to be used and are the least expensive. NNRTIs are increasingly being evaluated in pediatric treatment protocols. They are not associated with significant interactions with food; need to be taken once or twice daily and freely cross the blood brain barrier. Protease inhibitors are very efficacious but expense and side effects are major limiting factors. Details of commonly used drugs are listed in Table 1. Certain new drugs including NRTIs such as Abacavir, Adefovir and NNRTIs such as Efavirenz are also being evaluated in children (5).

COMMONLY USED ANTIRETROVIRAL IN CHILDREN

Drug	Dose	Side effects	Trade name	Practical points
NRTIs				
Zidovudine (AZT, ZDV)	Neonates-2 mg/kg 6 hourly children 90-180 mg/m2 6-8 hrly	Anemia, myopathy	Zidovir soln. 50mg/ml 100mg capsules, 300 mg tablets	Good CNS penetration Decrease dose if there is bone marrow suppression
Didanosine (ddI)	90mg/m3 12 hrly	neuropathy, pancreatitis, abd. pain , diarrhea		Administer empty stomach, space administration with protease inhibitors
Lamivudine (3TC)	4 mg /kg 12 hrly	Pancreatitis, neuropathy, neutropenia	Lamivir soln 50 mg / 5 ml Tablets 150 mg	Prevents emergence of zidovudine resistance
Stavudine (d4T)	1mg / kg 12 hrly	Headache,GI upset, neuropathy	Stavir capsule 30 mg, 40 mg	Should not be combined with AZT
NNRTIs				
Nevirapine (NVP)	120-200 mg/ m3 12 hrly	Skin rash, stevenjohnson syndrome	Nevimune 200 mg tablets	Start with 120 mg/m2 for 2 wks and then increase to full dose if no side effect
Protease Inhibitors				
Ritonavir	400mg/m2/12 hrly	Badtaste,vomiting, nausea, diarrhea	Norvir 80 mg / ml, capsules 100 mg	Start with 250 mg/m2 and then increase give with meals
Nelfinavir	20-30 mg / kg 8 hrly	Diarrhoea, abdominal pain		Give with meals
Indinavir	50mg/m2 8 hrly	Nephrolithiasis		Empty stomach, adequate hydration
Saquinavir	50 mg / kg / hrly	Diarrhoeal headache	Fortovase softgel cap	

			capsules	

Antiretroviral therapy provides significant clinical benefit in HIV infected children with immunologic or clinical symptoms of HIV infection with substantial improvements in neurodevelopment, growth, immunologic and/or virologic status (7). The efficacy of antiretroviral therapy in asymptomatic children has not been demonstrated. However given the pathophysiologic sequence of events in HIV infection, early aggressive therapy may help in preservation of the immune system and minimization of the risk of antiviral resistance. Moreover it has been found that infants and children have higher levels of plasma virus and more rapid disease progression as compared to adults (5).

Therefore the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children has proposed the following indications for initiation of antiretroviral therapy (8).

- Clinical symptoms associated with HIV infection (Categories A, B, C)
- Evidence of immune suppression (Immune category 2 or 3)
- Age < 12 months-regardless of clinical, immunologic or virologic status.

- For asymptomatic children > 1 year with normal immune status the preferred approach is to offer therapy to all. Alternatively treatment may be deferred and the virologic, immunologic and clinical status monitored. Therapy is initiated in the following circumstances.
- High or increasing HIV RNA copy number.
- Rapidly declining CD4 count/CD4 % approaching immune category 2.
- Development of clinical symptoms.

To simplify, the recent consensus is to use antiretrovirals in all HIV infected children irrespective of clinical, immunologic and virologic status (5).

Regimen of anti retroviral drugs :

- Preferred regimen :two NRTI plus one PI
- Recommended dual NRTI combinations: ZDV+ddI, ZDV+3TC, d4T+ddI, d4T+3TC,
- Protease inhibitors: RTV;NFV; IDV;SQV
- Alternate regimen:NVP+2NRTI
- Secondary Alternate regimen:2NRTI
- Not recommended: Any Monotherapy, d4T+ZDV,

As in adults, the combination of two NRTIs and one protease inhibitor is the preferred regime and comprises what is known as Highly Active Antiretroviral Therapy (HAART). Recommended NRTI combinations are zidovudine (ZDV) with didanosine (ddI) or ZDV and lamivudine (3TC). Limited data are available for combinations of stavudine (d4T) and ddI, d4T and 3TC, and ZDV and zalcitabine (ddC). Combinations of d4T with ZDV and ddC with ddI/d4T/3TC should be avoided. The protease inhibitors currently approved for infants and children are nelfinavir or ritonavir and indinavir for those who can swallow capsules (8).

Nevirapine with two NRTIs is an alternative and cheaper regime. The combination of only two NRTIs though of limited benefit can be offered when cost, non-availability or toxicity precludes the use of protease inhibitors (8). This combination results in significant clinical improvement, virologic and immunologic recovery and improves the quality of life although for a short time (7). The risk of resistance with such therapy in children is of a lesser concern, as they in usual circumstances do not pass on the resistant strains to others.

Monotherapy with any drug should be employed only for prevention of perinatal transmission and not for treatment purposes (8).

Monitoring and follow up:

On follow up the child should be evaluated for clinical improvement, compliance, adverse drug reactions as well as for rise in the CD4 counts and suppression of HIV RNA levels (Table 3). CD4 counts are estimated every three months. Plasma RNA determinations 4 weeks after initiating therapy and then 3 monthly are advocated. With a combination of two NRTIs a five-fold reduction of HIV RNA levels by 8-12 weeks is expected (8). With the standard regime of 2 NRTIs and a protease inhibitor, a ten-fold reduction is expected by 8-12 weeks and levels should be undetectable by 4-6 months (8). However since perinatally infected children have high baseline RNA levels, complete suppression is often not achievable unlike adults (5). In case of lack of optimal response, compliance, dosing schedule and possible drug interactions should be reviewed. If these are satisfactory and the lack of response is persistent, antiretroviral resistance should be suspected. Molecular techniques to identify mutations for the confirmation of resistance to antiretroviral drugs are under evaluation.

Madhivanan et al (9) and Merchant (10) and his colleagues in their studies conducted in India in 2001 reported that, Vertical transmission is responsible for between 67 and 87 per cent of paediatric HIV infection, with the majority of the remaining infections occurring due to blood transfusions.

The clinical features of HIV infection in children are different from those in adults. Perinatally infected children become symptomatic by five years of age. Failure to thrive is the most common clinical condition associated with HIV infection in children(9,10) Pulmonary and extrapulmonary tuberculosis was consistently the most frequent opportunistic infection reported in two major studies in Indian children with HIV. (9, 10)

Opportunistic infections (OIs) are an important cause of morbidity and mortality in children infected with HIV. However, few data are available regarding the overall prevalence, incidence and immunologic correlates associated with these diseases in the paediatric HIV population.

CD4 T-lymphocyte is the immune system cell that HIV infects and destroys, and the CD4 count roughly reflects the state of the immune system. Low CD4 T-cell counts are considered to be a marker of the progression of HIV infection and AIDS, and have been called the 'signature' of HIV (Balter 1997). Since HIV was first claimed to be the cause of AIDS in 1984, the CD4 count has been widely used to make treatment and diagnostic decisions, but the use of the CD4 count has been controversial, and recommendations regarding how to use them have changed many times over the years.

CD4 estimation is the backbone of AIDS control program in developing nations. It has been studied as a marker of progression of HIV infection and as a measure of relative

risk of developing opportunistic infections.HIV weakens the immune system so that opportunistic infections develop**.** Chakravarty et al, 2006 Indian study,(11)has showed children with opportunistic infection have lower CD4 values as compared to children without opportunistic infection . Ylitalo et al (12) h as also proved the same. Chakravarthy et al., 2006 Indian study (11) has showed CD4 percentage declining with progression in the WHO clinical stages of HIV infection.

The progression of disease is related to gradual disruption of lymph node architecture leading to high levels of viremia and disappearance of CD4 cells during later stages of disease. However, further studies of CD4 counts in relation to antiretroviral therapy in children needs to be done.

Fox- Wheeler et al (13) in his studies has showed ,HIV is associated with malnutrition. Similar observation has been reported in other studies as well**,** Shah and Bachou, Uganda, 2006. (14,15)

Agarwal, et al (16) in his studies conducted in Banaras Hindu university in 2005 has showed, CD4% correlated significantly with the deterioration of the WHO clinical stages and increasing grades of protein energy malnutrition .

Protein energy malnutrition leads to depletion of CD4 counts, and this is perhaps exacerbated by the presence of HIV infection. Protein energy malnutrition impacts the course of HIV by contributing to immuno-suppression.

Anniek et al (17) in his studies compared paediatric HIV in African settings to paediatric HIV in Western settings and to adult HIV in African settings. Several differences in diagnostic, clinical, immunological and virological characteristics were identified, as well as variations in the most influential factors for disease progression and response to ART. Environmental factors may influence disease progression, mortality, loss to follow-up, adherence and the need to adapt the regimen. The selected African paediatric programs recorded a higher increase in median CD4-percent than the selected Western paediatric programs and a higher increase in CD4-count than the selected African adult programs. Compared to the adult programs, the African paediatric programs had lower drop-out rates, higher reported adherence levels and comparable mortality rates. The Western paediatric programs, however, had the lowest mortality rates.

Pulmonary and extra pulmonary tuberculosis was consistently the most frequent opportunistic infection reported in two major studies in Indian children with HIV. Although frequencies differed, oral candidiasis, hepatosplenomegaly, recurrent respiratory tract infection, Pneumocystis carinii pneumonia, chronic lung disease, persistent generalized lymphadenopathy, chronic diarrhoea, pyrexia of unknown origin, chronic hypertrophic parotitis, chronic otorrhoea, bacterial skin infection, and PPE have also been reported in these studies.

PCP however, was seen much less commonly in Indian cohorts (3.4- 3.9%) than

Western cohorts where it is the most common AIDS diagnosis in infancy (18). Pneumocystis jerovecii causes severe pneumonia in patients with AIDS. Occurrence of PCP establishes the diagnosis of AIDS (19) and it is the most common AIDS-defining illness in the developed world. In India, however, very low rates (0.7 to 7%) 4, of PCP have been reported. Some reasons for this could be the predominance of other pulmonary diseases like TB, and due to under diagnosis of incident cases.. According to a large natural history study, Indian patients with PCP were 4.5 times more likely to die than patients without PCP. Median survival after diagnosis of PCP in this study was 24 months.

Bacterial pneumonia was reported as an opportunistic infection in 1.8 per cent of a large southern Indian cohort of HIV-positive patients. Similar to HIV negative individuals, the most common causes of acute community acquired pneumonia, are encapsulated bacteria, Streptococcus pneumonia and Haemophilus influenzae. Rates of bacterial pneumonia can be up to 25-fold higher among HIV infected children than in the general community. Although bacterial pneumonias can occur relatively early in the course of HIV, frequency of occurrence is inversely proportional to CD4 count.

Oral candidiasis occurs frequently in children with HIV infection; it has been reported as one of the most common HIV-associated condition, occurring in up to 70 per cent of cases. The pseudo membranous “white patches” variant of candidiasis is associated with more severe immunosuppression than the erythematous, hyperplastic or angular chelitis types.

Cryptococcal meningitis (CM) has been reported as the most common opportunistic infection of the CNS of Indian children with HIV. Poor prognostic factors for CM include positive blood cultures, altered mental status, CSF antigen titre above 1:1024, positive CSF India ink smear, CSF white cell count below 20cells/cu.mm, and elevated CSF pressures. Gold standard diagnosis of CM requires demonstration of organism in CSF.

TB meningitis in HIV children is different from HIV negative. Cognitive dysfunction is more common, and pathological features demonstrate reduced and atypical inflammatory responses, and extensive vasculopathy. There is absence of minimal meningeal enhancement and absence of communicating hydrocephalus on computed tomography (CT) scan in HIV-positive patients. As expected, mortality is higher in the HIV positive group.

Chronic diarrhoea is a major problem in HIV infected children, affecting up to 76 per cent of those with AIDS. It is associated with a 3.3 fold increased risk of disease progression. In reports from north, south and east India, Isospora belli and Cryptosporidium parvum were the two most common causes of chronic diarrhoeal disease in HIV infected children. Blastocystis hominis, Strongyloides stercoralis, Entamoeba histolytica, Giardia lamblia, enteropathogenic Escherichia coli, Enterocytozoon bieneusi and Campylobacter jejuni are other causative agents of diarrhoea in Indian patients with HIV. There was no geographic pattern to the frequency of organisms.

A variety of ocular conditions associated with AIDS in India have been reported: extensive blepharitis and spontaneous lid ulcer, extensive molluscum contagiosum CMV retinitis, herpes simplex keratitis, bilateral papilloedema with cryptococcal meningitis. The most common ophthalmic opportunistic infection in India is CMV retinitis, which almost always occurs in patients with CD4 counts <50 cells.

With the availability of antiretroviral therapy at lower cost, the clinical profile of HIV disease is now changing to include drug-related toxicities and immune reconstitution syndrome.

Immune reconstitution is of increasing concern in the developing world as HAART becomes more available in settings where opportunistic infections, especially TB, are abundant. The clinical presentation of IRS is an apparent clinical deterioration

of the patient despite treatment. This could indicate a successful, though undesirable, effect of HAART, or instead, treatment failure and subsequent progression of the opportunistic infection.

AIM OF THE STUDY

1. To study the clinical profile of pediatric HIV.

2. To correlate the clinical profile with CD4 values.

3. To analyse the outcome and the response to ART in relation to CD4

MATERIALS & METHODS

- Setting

  Study was conducted in Institute of child health and research centre-Government Rajaji hospital, Madurai.

- Collaboration Departments

  The study was done in collaboration with ART centre, Department of Microbiology, Department of Pathology , GRH,Madurai.

- Ethical committee

  Approval for the study was obtained from The Ethical committee of Govt. Rajaji Hospital.

- Study design

  Prospective cross sectional analytical study

- Study period

  The study period was from **June 2006-July 2008**

■ Sample size

A total of 355 children which included all children enrolled in ART centre, Government Rajaji Hospital, Madurai.

Inclusion criteria:

1. Newly diagnosed HIV positive children >18 months up to 15 Years.
2. Children < 18 months with positive DNA PCR

Exclusion criteria:

1. Children previously on ART

The study was conducted prospectively from June 2006 to July 2008 (26 months) and included children (aged 1 month to 15 years) admitted consecutively to the pediatric wards with the diagnosis of HIV infection. Children were tested for HIV if they had one or more of the following manifestations: prolonged unexplained fever, chronic diarrhea, generalized lymphadenopathy, recurrent systemic infections, septicemia or failure to thrive. Informed consent was obtained from the parent/guardian

for the HIV testing with appropriate pre and post-test counseling. ELISA testing for HIV antibodies was performed for establishing the diagnosis. If detected to be positive, confirmation was done by two more ELISA tests. Children less than 18 months of age underwent confirmation by DNA-PCR testing. HIV status of the parents and siblings of the affected children was also requested (after appropriate counseling).

Definitions of Clinical factors studied :

Asymptomatic :

No HIV related symptoms reported and no signs on examination.

Persistent generalized lymphadenopathy (PGL) :

Swollen or enlarged lymph nodes > 1 cm at two or more non contiguous sites, without known cause.

Unexplained persistent hepatosplenomegaly :

Enlarged liver and spleen without obvious cause

Papular pruritic eruptions :

Papular pruritic vesicular lesions. Scabies and insect bites should be excluded.

Fungal nail infections :

Fungal paronychia (painful, red and swollen nail bed) or onycholysis (painless separation of the nail from the nail bed). Proximal white subungual onchomycosis is uncommon without immunodeficiency.

Angular cheilitis :

Splits or cracks on lips at the angle of the mouth with depigmentation usually responding to antifungal treatment but may occur.

Lineal Gingival Erythema : (LGE)

Erythematous band that follows the contour of the free gingival line ; may be associated with spontaneous bleeding.

Extensive wart virus infection :

Characteristic warty skin lesions ; small fleshy grainy bumps, often rough, flat on sole of feet (plantar warts), facial, more than 5% of body area or disfiguring.

Extensive molluscum contagiosum infection :

Characteristic skin lesions : small flesh coloured, pearly or pink, dome-shaped or umbilicated growths, may be inflamed or red ; facial, more than 5% of body area or

disfiguring.

Recurrent oral ulcerations (two or more in six months) :

Aphthous ulceration, typically with a halo of inflammatio and yellow grey pseudo membrane.

Unexplained parotid enlargement :

Asymptomatic bilateral swelling that may spontaneously resolve and recur, in absence of other known cause, usually painless.

Herpes zoster :

Painful rash with fluid filled blisters, dermatomal distribution, can be haemorrhagic on erythematous background, and can become large and confluent. Does not cross the midline.

Recurrent upper respiratory tract infection (URTI) :

Current event with atleast one episode in past 6 months. Fever with unilateral face

pain and nasal discharge (sinusitis) or painful swollen eardrum (ortitis media), sore throat with productive cough (bronchitis) sore throat (pharyngitis) and barking croup like cough (LTB). Persistent or recurrent ear discharge.

Unexplained moderate malnutrition :

Weight loss : low weight for age, up to 2 standard deviations (SDs), not explained by poor or inadequate feeding and or other infections and not adequately responding to standard management.

Confirmed by documented loss of body weight of -2 SD, failure to gain weight on standard management and no other cause identified during investigation.

Unexplained persistent diarrhoea :

Unexplained persistent (14 days or more) diarrhoea (loose or watery stool, three or more times daily), not responding to standard treatment). Confirmed by stools observed and documented as unformed. Culture and microscopy reveal no pathogens.

Unexplained persistent fever (intermittent or constant, for longer than one month)

Reports of fever or night sweats for longer than one month, either intermittent or constant, with reported lack of response to antibiotics or anti malarials. No other

obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas. Confirmed by documented fever of > 37.5 C with negative blood culture, negative malaria slide and normal or unchanged CXR, and no other obvious foci of disease.

Oral Candida : (outside first 6-8 weeks of life)

Persistent or recurring creamy white to yellow soft small plaques which can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythmatous form).Confirmed by microscopy or culture.

Oral hairy leukoplakia :

Fine small linear patches on lateral borders of tongue, generally bilaterally, which do not scrape off.

Lymph node TB :

Non acute, painless "cold" enlargement of lymphnodes, usually matted, localized to one region. May have draining sinuses. Response to standard anti-TB treatment in one month. Confirmed by histology or fine needle aspirate for Ziehl Neelsen stain/Culture.

Pulmonary TB :

Nonspecific symptoms, eg. Chronic cough, fever, night sweats, anorexia and weight loss. In the older child also productive cough and haemoptysis. Abnormal CXR. Response to standard anti – TB treatment in one month. Confirmed by positive sputum smear or culture.

Severe recurrent presumed bacterial pneumonia :

Cough with fast breathing, chest indrawing, nasal flaring, wheezing and grunting. Crackles or consolidation on auscultation. Responds to course of antibiotics. Current episode plus one or more in previous 6 months.

Confirmed by isolation of bacteria from appropriate clinical specimens (induced sputum, BAL, lung aspirate).

Acute necrotizing ulcerative gingivitis or stomatitis, or acute necrotizing ulcerative periodonitis.

Severe pain, ulcerated gingival papillae, loosenig of teeth, spontaneous bleeding, bad odour, and rapid loss of bone and or soft tissue.

Symptomatic LIP : Diagnosed by CXR : bilateral reticulo nodular interstitial

pulmonary infiltrates present for more than two months with no response to antibiotic treatment and no other pathogen found. Oxygen saturation persistently < 90%. May present with corpulmonale and may have increased exercise induced fatigue. Characteristic histology.

Chronic HIV associated lung diseases (including bronchiectasis)

History of cough productive of copious amounts of purulent sputum (bronchiectasis only), with or without clubbing, halitosis, and crepitations and or wheezes on auscultation.

Confirmed by CXR may show honeycomb appearance (small cysts) and / or persistent areas of opacification and / or widespread lung destruction, with fibrosis and loss of volume.

Unexplained anaemia (<8g/dl) or neutropenia (<1000/mm3) or chronic thrombocytopenia (< 50000/mm3):No presumptive diagnosis. Diagnosed on laboratory testing, not explained by other non HIV conditions, or not responding to standard therapy with haematinics, antimalarials or antihelminthics as outlined in MCI.

Unexplained severe wasting, stunting or severe malnutrition (not adequately responding to standard therapy.)

Persistent weight loss not explained by poor or inadequate feeding, other infections and not adequately responding in two weeks to standard therapy. Characterised by : visible severe wasting of muscles with or without oedema of both

feet, and or weight for height of 3 SDs as defined by WHO IMCI guidelines.

Confirmed by documented weight loss of > -3 SD +/- oedema

Pneumocystis pneumonia PCP :

Dry cough, progressive difficulty in breathing, cyanosis, tachypnoea and fever ; chest indrawing or stridor. (Severe or very severe pneumonia as in IMCI). Usually of rapid onset especially in inflants under six months of age. Response to high dose co-trimoxazole +/- prednisolone. Confirmed by : CXR typical bilateral perihilar diffuse infiltrates ; microscopy of induced sputum or BAL or NPA, or histology of lung tissue.

Recurrent severe presumed bacterial infection, eg. Empyema, pyomyositis bone or joint infection, meningitis but excluding pneumonia. Fever accompanied by specific symptoms of signs that localize infection. Responds to antibiotics. Current episode plus one or more in previous 6 months. Confirmed by culture of appropriate clinical specimen.

Chronic herpes simplex infection : (orlabial or cutaneous of more than one month's duration or visceral at any site). Severe and progressive painful oralabial, genital, or anorectal lesions caused by HSV infection present for more than one month. Confirmed by culture and / or histology

Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs). Chest pain and dysphagia (difficulty in swallowing), odynophagia (pain on swallowing food and fluids) or retrosternal pain worse on swallowing (food and fluids) responds to specific treatment. In young children, suspect particularly if oral candida observed and food refusal occurs and / or difficulties / crying when feeding. Confirmed by macroscopic appearance at endoscopy, microscopy of specimen from tissue or macroscopic appearance at bronchoscopy or histology.

Extrapulmonary / disseminated TB :

Systemic illness usually with prolonged fever, night sweats, weight loss. Clinical features of organs involved, eg. Sterile pyuria, pericarditis, ascites, pleural effusion, meningitis, arthritis, orchitis. Respods to standard anti TB therapy. Confirmed by positive microscopy showing AFB or culture of Mycobacterium tuberculosis from blood or other relevant specimen except sputum or BAL, biopsy and histology.

IAP (Indian Academy of Paediatrics) grading of malnutrition :

Grade I - 71-80% of expected weight for age

Grade II - 61-70% of expected weight for age

Grade III - 51-60% of expected weight for age

Grade IV - less than 50% of expected weight for age.

Clinical details were recorded including demo-graphic details, possible modes of transmission, presenting symptoms, nutritional status and opportunistic infections at the time of presentation. Opportunistic infections were diagnosed using the standard protocol. Baseline CD4 lymphocyte counts were determined by FACS count. Based on the clinical presentations, the children were categorized into various WHO clinical stages (I to IV) (3). Weight for age was used to grade them (IAP classification) for protein energy malnutrition (4). They were further classified based on CD4% values in accordance with WHO classification of immunodeficiency (3). CD4 cell count varies with age so CD4% was used to define immunologic category (5). Antiretroviral therapy was started according to National AIDS Control Organization (NACO) guidelines (3). Patients were followed up every month and CD4 counts were repeated at 6 monthly interval.

Pulmonary tuberculosis was diagnosed on the basis of positive Manteoux test (erythema and induration 5 mm), chest radiograph, screening of family members for tuberculosis, nonresponse to conventional antibiotic therapy and good response to antitubercular drugs. Tuberculosis was managed as per RNTCP guidelines**.** Additionally, tuberculosis of the lymph nodes was diagnosed on the basis of aspiration

cytology or excision biopsy while abdominal tuberculosis was diagnosed on the basis of findings on ultrasonography of the abdomen and also barium studies.

HIV encephalopathy was diagnosed on the basis of clinical features, neuroimaging findings, CSF (cerebrospinal fluid) studies and exclusion of other processes causing similar clinical manifestations. HIV cardiomyopathy was recognized by virtue of the color Doppler findings. Patients were treated symptomatically based on their clinical presentation. Opportunistic infections were treated adequately and appropriate prophylaxis was administered for prevention of recurrence of opportunistic infections. **(**8).All exposed infants were prescribed cotrimoxazole prophylaxis from 6 weeks of age. Older children were prescribed cotrimoxazole only if ART eligibility criteria were met. First-line drugs include zidovudine or stavudine plus lamivudine plus nevirapine or efavirenz. Where possible, children with hemoglobin levels less than 10 g/dL were not prescribed zidovudine. Nevirapine was used preferentially in all children, while efavirenz was reserved for those requiring concurrent treatment with rifampicin or not tolerating nevirapine. After treatment initiation, patients were under observation for 2 weeks. At each visit, peer counselor & ART counselor performs an adherence assessment. These adherence counselling sessions were also used to provide and education regarding drug adverse effects.

All clinical data pertaining to the study subjects were entered in the EXCEL

worksheet at every follow up visit .Data were then analysed. One way ANOVA (analysis of variance) test was used to compare the means and Fisher's exact/ Chi square test for categorical variables.

Changes in the weight, CD4 count, CD4% at the baseline and at 6 months follow up visit were compared using paired t test.

RESULTS

During the study period, 355 children were screened positive for HIV infection. Their demographic profile is given in Table I.

The mean age of first presentation was 4.5 years (0-15 years). Vertical transmission was the assumed mode of transmission in 97% children in view of maternal seropositivity. Blood transfusion was considered the cause of infection in 1 child (received transfusion from his distant relative). Multiple injections was presumed mode in 2 children (history of injection at village hospitals).

Fever was the most common presenting symptom (42%), followed by cough (38%), chronic diarrhea (26%), skin manifestations (26%), generalized lymphadenopathy(22%) hepato-splenomegaly (22%) and other manifestations(12%).

One third of the children were asymptomatic. CD4% declined with deterioration of WHO clinical stages of the disease (Table II). Protein energy malnutrition was present in 82% children. Mean CD4 percentage was 42.6%±10.7 in children without malnutrition (18%). Mean CD4 percentage was 18%±9.7 in children with some degree of malnutrition (82%) The various grades of protein energy malnutrition with their corresponding mean CD4 values are given in Table III. The correlation of severity of malnutrition with decline in CD4 percentage was significant (P<0.05).

One hundred and twenty one children (30%) had opportunistic infections at the time of evaluation. Patients with opportunistic infections had lower CD4 values (12.9%±9.4) as compared to patient without any opportunistic infections (28.4% ±8.6). Tuberculosis was the most common opportunistic infection. Disseminated tuberculosis and pneumocystis pneumonia and CMV retinitis had the least CD4 values.

Pruritic skin lesions, anemia, hepatosplenomegaly and lymphadenopathy and tuberculosis were commonly noticed in older children. Serious life threatening illness like pyogenic meningitis, recurrent bronchopneumonia, pneumocystis pneumonia and recurrent diarrhea were observed in preschoolers and infants.

Tuberculosis was present in 54 cases. (pulmonary 21, extrapulmonary 33). Out of 33 extra-pulmonary, 30 were TB lymphadenopathy,2 were TB meningitis, 1 Disseminated TB. Out of 54 Tuberculosis cases, manteaux was positive in 21 cases, sputum positive for AFB in 2 cases. 5 out of 15 deaths were (33% mortality) due to tuberculosis. (overall mortality 4.2%).

134 children, in whom Antiretroviral therapy was started & followed up for atleast 6 months, 119 were alive and on follow up.

There were 15 deaths. The median age at ART initiation was 54 months, with 6 children (9.9%) younger than 11 months, 27 (28.6%) aged 11 to 36 months, and 33 (36-59 months),68 children (60 months –15 yrs).

Of those 134 (WHO stage II – 18 , stage III- 54, stage IV -62), who started on ART, the median age was 4.5 yrs, 81 were male and 53 were female. The mean weight(SD)at the baseline was14.3 (6.64) and increased to 16.58 (7.19) at the last follow up visit. The mean CD4 cell (SD) percentage at ART initiation among the 119 children was 13.47(4.25) % and increased to 25.51(6.9)% at the last follow up. Median Hemoglobin was 8.6 at the base line and 9.4 gm % at the last visit . Fifteen children died over 2 years of follow-up. Two children failed to respond to first line ART regimen and were considered as treatment failure. They were referred for second line ART regimen.

In our study, Out of 134 children starting ART,102(76.11%) began stavudine plus lamivudine plus nevirapine, 3(2.2%) began zidovudine plus lamivudine plus nevirapine, 2 (1.49%) began zidovudine plus lamivudine plus efavirenz, and 27 (20.14%) began stavudine plus lamivudine plus efavirenz because 27 cases were screened positive for tuberculosis initially. Of patients starting a nevirapine-based regimen, 4 were switched to efavirenz ,because of allergy. Of patients starting a Zidovudine-based regimen, 2 were switched to stavudine, as they developed anemia.

Thirteen patients (9.7%) had adverse effects related to the ART. 4(2.9%) patient had severe gastritis. (1 on Zidovudine and 3 on stavudine regimen) initially which subsided with treatment. Two patients (1.4%) had hepatotoxicity which succumbed due to TB meningitis. 2 patient (1.4%) had zidovudine (AZT) induced anemia, 4 patients (2.9%) had Nevirapine (NVP) induced rash, 1 patient (0.7%) had Stavudine (d4T) induced Peripheral neuropathy.

Out of 355 children, 15 (4.2%) died,. Children who died were younger compared to those who survived, (median age, 36 months vs 60 months; P < .001), had lower mean weight (10.0 vs 13.96 P < .001), had lower baseline median hemoglobin concentration (8.4 g/dL vs 9.2 g/dL; P < .001), were more likely to be WHO clinical stage IV (100% vs 14%, P < .001), had lower baseline CD4 values (15.7%

vs18.8%) compared to those who survived. Mortality was associated with younger age, lower weight-for-age, anemia WHO stage IV and CD4 cell depletion

TABLE I

DEMOGRAPHIC PROFILE OF HIV INFECTED CHILDREN

Variables	Number	Mean CD4% ±SD	WHO classification immunodeficiency			
			Not significant	Mild	Advanced	Severe
Gender						
Male	199(56.05)	18.8	52(26.1)	64(32.1)	43(21.6)	40(20.1)
Female	156(43.94)	21.5	60(38.4)	45(28.8)	25(16.0)	26(16.6)
Age in years						
0≤1 yr	45(2.67)	21.0±2.69	21(46.6)	20(44.4)	2(4.4)	2(4.4)
1 ≤3yr	95(26.76)	21.6±7.6	44 (46.31)	24(25.26)	14(14.73)	13(13.68)
3 ≤6yr	92(25.91)	18.9± 8.2	34 (36.95)	25(27.17)	16(17.39)	17(18.47)
6≤9yr	41(11.54)	17.2± 9.5	11(26.82)	4 (9.7)	17(41.46)	9 (21.95)
9 ≤12yr	48(13.52)	15.8± 6.9	15 (31.25)	11(22.91)	14(29.16)	8(16.66)
12 ≤15yr	34 (9.57)	12.3± 4.5	9(26.47)	5(14.70)	11(32.35)	9(26.47)

TABLE II

CD4 CORRELATION WITH CLINICAL PROFILE OF HIV INFECTED CHILDREN

Variables	Number	Mean CD4%±SD
WHO clinical staging		
I	121(34.08%)	26.9±10.2
II	114(32.11%)	20.4±6.4
III	54(15.21%)	16.0±8.2
IV	66(18.59%)	12.6±9.0
PEM** (IAP grading)		
Grade I	56(15.77%)	24.2±8.1
Grade II	99(27.88%)	22.7±8.2
Grade III	75(21.12%)	14.8± 9.4
Grade IV	62 (17.46%)	10.2±6.7

Oppurtunistic infections	Number	Mean CD4%±SD
Anaemia Hb % > 14 12 – 14 10 – 12 8 - 10 <8	 10 (2.8%) 36(10.1%) 72 (20.3%) 232(65.3%) 5 (1.4%)	 36±6.2 32±6.2 26±8.2 24±8.4 12.0±3.4
Tuberculous lymphadenopathy :	30(8.4%)	26±8.6
lymphadenopathy	78(21.9%)	32±7.2
Thrombocytopenia	1(0.2%)	12
papullar pruritic eruptions :	53(14.9%)	36±11.2
viral warts :	20(5.6%)	28±8.6
Molluscum contagiosum	22(6.1%)	11±5.4
Seborrhoeic Dermatitis	20 (5.6%)	26±6.2
Scabies	17(4.7%)	26±7.4
Chicken pox	14(3.9%)	16±5.6
Herpes zoster	7(1.9%)	24±7.4
Ulcerative gingivitis/periodontitis	28(7.8%)	14±6.2
Oral candidiasis	18(5.0%)	9±7.2
Chronic parotitis	12 (2.5%)	20±3

Chronic /Recurrent Diarrhoea	91(25.6%)	22±8.4
Hepatosplenomegaly	79(22.2%)	21±8.1
Cryptosporidiasis	16(4.5%)	11±6.2
Pulmonary Tuberculosis	21(5.9%)	16±7.4
Bacterial Pneumonia	30(8.4%)	18±8.4
Pneumocystis carinii pneumonia	2(0.5%)	3.5±0.5
Lymphoid interstitial pneumonia	1 (0.2%)	15.5
Chronic lung disease	3(0.8%)	12±2
CSOM/Otorrhoea	46(12.9%)	25±5.5
Recurrent Upper Resp. Infection	96(27.0%)	24±6.4
Tuberculous Meningitis	2(0.5%)	8±2.0
Pyogenic Meningitis	2(0.5%)	12±2.0
HIVEncephalopathy/Developmentaldelay	10(2.8%)	10±2.5
CMV Retinits	2(0.5%)	5±0.5
Cardiomyopathy	1 (0.28%)	12.4

Table-III

COMPARISON OF CD4 BEFORE AND AFTER ART

	Before treatment (n=134)	**At followup (n=119)**	**p- value**
Mean CD4 count	427(306)	1095(470)	0.001
Mean CD4 %	13.47(4.25)	25.5(6.90)	0.001
Median hb	8.6	9.4	0.001

Table-4

AGE WISE CHANGE IN WEIGHT AND CD4 COUNT AFTER ART

	Initial	At follow up	p-value
Age <11months			
Weight	5.66(1.15)	6.75(0.66)	0.23
CD4 count	1076 (284.02)	1545 (478.5)	0.31
CD4%	19.94(7.10)	31 (7.93)	0.11
Age12-36month			
Weight	7.48 (2.023)	9.26(1.932)	0.0001
CD4 count	750.64(299)	1306(356)	0.0001
CD4%	16.28 (3,37)	25.9 (4.9)	0.0001
Age36-59months			
Weight	11.72 (2.19)	14.13 (2.48)	0.0001
CD4count	411.76(132.7)	1206.31(518.6)	0.0001
CD4%	13.16 (3.08)	27.13(4.65)	0.0001
Age>60months			
Weight	19.45 (5.83)	22.18 (6.2)	0.0001
CD4	241.5(12)	1065(350.64)	0.0001
CD4%	11.97(3)	27.48(5.1)	0.0001

Table – 5

AGE WISE MORTALITY

AGE GROUP	(n)	6 months Survival	Mortality (%)
11 months	6	50%	3 (50%)
11 to 35 months	27	71%	8 (29.6%)
36-59 months	33	97%	1 (3.0%)
60 mon –15 yr	68	95.6%	3 (4.4%)

Table -6

FACTORS ASSOCIATED WITH MORTALITY

	Death	Survived	p value
Rate	4.2%	95.2%	0.001
Median age (months) at presentation	36	60	0.001
Mean weight	10.0	13.96	0.001
Baseline Hb gm	8.4	9.2	0.001
WHO stage iv	100%	14%	0.001
Baseline CD4%	15.7%	18.8%	0.001

DISCUSSION

This prospective cross-sectional study has analysed the clinical profile in relation to CD4 status in HIV infected children attending our ART centre.

Clinical features in HIV-infected children in our study had some similarities and few differences from the previous Indian studies(20,21,22,23,24,25,26).

Table 6and 7 compare demographic data and clinical features of our study with those of previously reported Indian studies.

Demo graphic	Daga data et al. (12)	Dhurat et al. (4)	Lodha et al. (13)	Mercha nt et al. (5)	Karande et al. (7)	Madhi vanan et al. (8)	our
Total number	**28**	**55**	**27**	**285**	**24**	**58**	**355**
Males	**18 (64.3%)**	**28 (50.9%)**	**20 (74.1%)**	**–**	**13 (54.2%)**	**39 (67.2%)**	**199 (56%)**
Females	**10 (35.7%)**	**27 (49.1%)**	**7 (25.9%)**	**–**	**11 (45.8%)**	**19 (32.8%)**	**156 (44%)**
Mean age at Presen tation	**10 months**	**2month–13ys**	**4.5 ys**	**213 (74.7%)**		**4 years**	**4.5 yrs**
Follow-up	**10–18 months**	**9 months**	**–**	**–**	**–**	**–**	**2 years**

COMPARISION OF CLINICAL PROFILE WITH OTHER STUDIES

Demo graphic	Dagadata et al (12)	Dhurat et al (4)	Lodha et al (13)	Merchant et al (5)	Karande et al (7)	Madhi vanan et al (8)	Our study
Tuberculosis	08 (28.5%)	27 (49%)	13 (48.1%)	84 (29.4%)	11 (45.8%)	24 (41.37%)	54 (15.2%)
MT positivity	04	0	–	–	–	-	21
PCP	–	–	–	11 (3.8%)	–	2 (3.44%)	2
Oral candidiasis	06 (21.4%)	13 (23.6%)	08 (29.6%)	42 (14.7%)	13 (54.1%)	–	48 (13.5%)
Severe PEM (IAP grades III & IV)	(60.7%)	19 (34.5%)	22 (81.4%)	127 (44.5%)	19 (79.1%)	10 (17.24%)	13 7 (35.5%)
Skin manifstn.	03 (10.7%)	16 (29%)	–	63 (22.1%)	–	–	92 (25.9%)
Hepato Splenomegaly	–	20 (36.3%)	18 (66.6%)	82 (28.7%)	–	8 (13.79%)	77 (21.6%)
Generalized – lymph adenopathy	–	13 (23.6%)	09 (33.3%)	67 (23.5%)	–	8 (13.79%)	78 (22%)
HIV encephalopathy/ CNS involvement		–	03 (11.1%)	13 (4.5%)		-	14 (3.9%)
Fever –	–		21 (77.7%)	36 (12.6%)	–	–	149 (42%)
Death	10 (35.7%)	14 (25.4%)	–	30 (10.5%)		8 (13.79%)	15 (4.2%)
Age at death Median:	Median: 18 months	8.5 months in perinatally acquired (0.3 months to 2 years	–	–	–	–	1.75yrs (range 6 months -7 years)
Causes of death	04-Multiorgan failure 04-Unknown	–		07-HIV-encephalopathy 05-disseminated TB 03-Neurotuberculosis02-gr-IV PEM 02-PCP 02-Fungal sepsis			HIV encephal-04 pyogenic meningit-03 TB mening-02 Pneumonia(including one TB)& sepsis -05 Chronic lung disease -1

As in the previous series, perinatal transmission was the most common mode of transmission in our study. HIV acquired via sexual abuse has been reported previously (21) but was not encountered by us.

Daga et al(25)reported the presence of known HIV infection in one/both parents in 7 cases.

Growth retardation is a common feature in HIV infected children. Weight gain has been used as a parameter in assessing the improvement in clinical status in many studies(14)**.** Somatic growth has shown to be affected in patients with HIV infection (28). 82% of our children had some degree of PEM (Grade I to IV of IAP). 137 children (39%) in our series had severe malnutrition (grade III/IV) and 155 others (43%) had mild malnutrition (grade I/II). This may be caused by various factors such as poor nutrition, neglect, poverty, repeated infections, etc. Malnutrition has been reported to be the most common manifestation in HIV-infected children (21,22,23).

Hepatomegaly was seen in 22% of our cases and was one of the most common manifestations in our study. Hepatomegaly can be caused by the replication of the HIV within the reticuloendothelial system and early onset lymphadenopathy and hepatomegaly in the first 3 months of life is associated with rapid disease progression (28). Hepatosplenomegaly was seen in 28.7% of cases in the study by Merchant et al.

(22) and in 36% of the cases studied by Dhurat et al. (21).

Generalized lymphadenopathy was seen in 22% of our patients and may have been the result of viral infections (such as Epstein-Barr virus or cytomegalovirus), opportunistic infections, and mycobacterial infections apart from being caused by the HIV infection (28). Persistent generalized lymphadenopathy has been seen in 23.5% of cases by Merchant et al. (22).

In the present study, diarrhea was the presenting manifestation in 22% children,. Infections causing diarrhea in HIVinfected children include rotavirus, Shigellae, Campylobacter, E. coli, cryptosporidiosis, isosporiasis, cytomegalovirus and atypical mycobacteria (22,28). Cryptosporidiosis was reported in 16 cases.Chronic/recurrent diarrhea has been seen in 15 to 43% cases in various studies 22,23,25)

We encountered tuberculosis in 54 cases (15%). (pulmonary 21, extrapulmonary 33). Out of 33 extra-pulmonary, 30 were TB lymphadenopathy, 2 were TB meningitis ,1 Disseminated TB. Out of 54 Tuberculosis cases, manteaux was positive in 21 cases, sputum positive for AFB in 2 cases**.** Pulmonary tuberculosis occurred between wide range of CD4 values ranging from 2% to 30%. TB meningitis occurred with low CD4 values (4% to 12%).

Tuberculosis in various forms—pulmonary and extrapulmonary has been reported commonly in HIV-infected children(21,22,23,25,26) One cannot depend on the

Mantoux (tuberculin) test as it may be falsely negative in patients with HIV (25). Only four of eight children diagnosed to have tuberculosis had positive Mantoux test in the study by Daga et al. (25). Twenty one patients had positive Mantoux test in our study. As in other studies, lack of culture facilities have made it difficult for us to study the presence of atypical mycobacteria and resistance pattern in HIV-infected children (22). Merchant et al. reported 84 cases (29.4%) with tuberculosis in a cohort of 285 cases; of whom 48 had pulmonary lesions, 21 had disseminated tuberculosis, 8 had tubercular lymphadenopathy and 7 had neurotuberculosis (22). Dhurat et al. have reported pulmonary tuberculosis in 16 cases, 9 extrapulmonary (of whom 4 had pulmonary tuberculosis as well; extrapulmonary sites: abdominal-4, neurotuberculosis- 2 and lymphadenopathy-3 cases) (21). A similar spectrum of tubercular manifestations was seen in our study as well.

3 cases of Bronchiectasis were encountered in our study (4,5,9),as reported in earlier studies. Bronchiectasis occurred when the CD4 is around 12% (severe immunosuppression).

Pneumocystic carinii pneumonia was less common in our study. Pneumocystis carinii pneumonia (PCP) was present in two cases. Merchant et al. have reported 11 cases of PCP (22). A low incidence of PCP has been reported among our children . Whether the apparent differences in the occurrence of *P. carinii* pneumonia reflect difficulties in establishing the diagnosis, differences in disease susceptibility or

geographic variation in the prevalence of the organism needs to be explored.

Lymphoid interstitial pneumonia was seen in only one patient in our study.

Dermatological manifestations were common in our study(26%). Papular pruritic eruptions (15%) were the most common skin lesion encountered in our study. Seborrheic dermatitis(5.6%), scabies(4.7%), drug eruptions, and skin lesions associated with nutritional deficiencies, herpes zoster(2%), molluscum contagiosum(6%), viral warts(5.6%) were also noted. PPE occurred in CD4 ranging from (25 to 36%). Mollucum contagiosum had the lowest CD4 (11%) compared to all other cutaneous conditions. Skin lesions including herpes zoster (19 cases), chronic nonspecific dermatitis (20 cases), scabies (18 cases), pyoderma (15 cases), molluscum contagiosum (3 cases) and chronic paronychia (2 cases) have been reported by Merchant et al. (22). Similarly, Dhurat et al. have reported seborrheic dermatitis (6 cases), chicken pox (4 cases; hemorrhagic in 2 cases) and herpes zoster (2 cases) (21).

Anemia was seen in 66% of cases in our study. The causes may include bone marrow changes consistent with anemia of chronic disorders, nutritional deficiency (folic acid or vitamin B12), adverse effects of medications and peripheral destruction of erythrocytes (28). Anemia has been noted in symptomatic patients in the study by Dhurat et al. (21) (32%) and Merchant et al. (22). Thrombocytopenia was reported in one case.

HIV-encephalopathy has been reported in up to 21% of cases with HIV infection

in other studies (28). Merchant et al. had 13 cases with HIV encephalopathy in their series (22). 3% of our patients had HIV-encephalopathy. The neuroimaging features (cerebral atrophy, infarction, calcification) were also consistent with the diagnosis of encephalopathy in these patients. Clinical and neuroimaging features of HIV-encephalopathy were similar to the studies reported earlier (22,29). Presence of HIV-encephalopathy is associated with poor outcome for survival (22,29).

Cardiomyopathy was seen in one case in the present study. One case of immune reconstitution syndrome was encountered and managed appropriately.

12 cases of parotitis were encountered in our study. All oral conditions occurred in CD4 range of moderate immuno deficiency (15-25%), except oral candidiasis which occurred in CD4 values of severe immunodeficiency.

As in some of the previous studies, no cases with renal manifestations and malignancies were reported in our study (21,22,28)

CD4 count was used as a measure of Immunological outcome in previous studies.(31,32)WHO & national guidelines advise that clinicians use CD4 cell percentage for assessment of children younger than 60 months and absolute CD4 cell count for children 60 months or older. Significant improvement in the CD4 count and CD4% in response to ART illustrated in our study is in accordance with previous studies.(31,32)

Thirteen patients (9.7%) had adverse effects related to the ART. 4(2.9%) patient had severe gastritis.(1 on Zidovudine and 3 on stavudine regimen) initially which subsided with treatment. Two patients (1.4%) had hepatotoxicity which succumbed due to TB meningitis. 2 patient (1.4%) had zidovudine (AZT) induced anemia, 4 patients (2.9%) had Nevirapine (NVP) induced rash, , 1 patient (0.7%) had Stavudine (d4T) induced Peripheral neuropathy. Hepatotoxicity was far less in the present study in view of close monitoring and careful selection of cases. This is in contrast to previous Indian study which reported high incidence of hepatotoxicity.(33)

Table -9

COMPARISION OF DRUG TOXICITIES WITH OTHER INDIAN STUDY

Toxicity	Drug	Present study(%)	Irashahetal mum2005(%)
incidence	OVERALL	9.7	30
gastritis	zidovudine	2.9	-
hepatotoxici	Stavu/nevi	1.4	16
anemia	zidovudine	1.4	12
Rash/SJS	nevirapine	2.9	9
Peri.neurop.	Stavudine	0.7	-

Out of 355 children, 15 (4.2%) died,. Children who died were younger compared to those who survived, (median age, 36 months vs 60 months; P < .001), had lower mean weight (10.0 vs 13.96 P < .001), had lower baseline median hemoglobin concentration (8.4 g/dL vs 9.2 g/dL; P < .001), were more likely to be WHO clinical stage IV (100% vs 14%, P < .001), had lower baseline CD4 values (15.7% vs18.8%) compared to those who survived. Mortality was associated with younger age, lower weight-for-age, anemia WHO stage IV and CD4 cell depletion

Mortality has been variably reported to be 10.5% (22), 25.4% (21) and 35.7% (25) in various studies. Fifteen of our patients (4.2%) died in our study. These differences in figures may reflect the differences in the clinical manifestations, early versus late presentations, duration of follow-up, presence of opportunistic infection, appropriate intervention with antiretroviral therapy, availability of ancillary and supportive care, nutritional support etc. in our centre.

CONCLUSION

- HIV disease in children has a diverse range of manifestations in multiple organ systems.
- Fever is the most common initial presentation in children followed by cough and diarrhoea.
- Pulmonary tuberculosis is the most common opportunistic infection followed by oral candidiasis.
- Meningitis, CMV retinitis, Pneumocystis carinii pneumonia,oral candidiasis, grade IV malnutrition, WHO class IV symptoms correlate with very low CD4%.
- Treatment with ART results in improvement in CD4%.
- Mortality is associated with younger age, lower weight-for-age, anemia, WHO stage IV and CD4 cell depletion

LIMITATIONS

- Viral assays which remains the most sensitive indicator of response to antiretroviral therapy could not be done because of cost concerns.
- Protease inhibitor-based therapy remains very expensive and unaffordable to our patients.

RECOMMENDATIONS

- To suspect and recognize symptoms & signs of HIV early in infancy to start ART earlier.
- Early institution of ART in infancy to reduce underfive mortality due to HIV.
- In the new era of generic HAART, physicians must be trained to identify and manage the toxicities associated with HAART .
- Interventions should focus on both child and caregivers and must address social problems that adversely affect adherence.
- Physicians and health care professionals should be taught about Universal precautions and post-exposure prophylaxis

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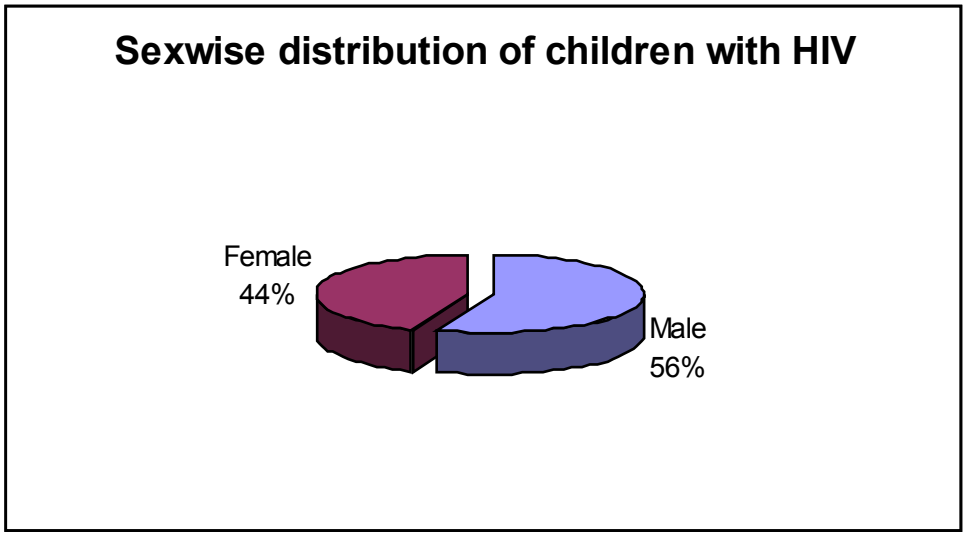
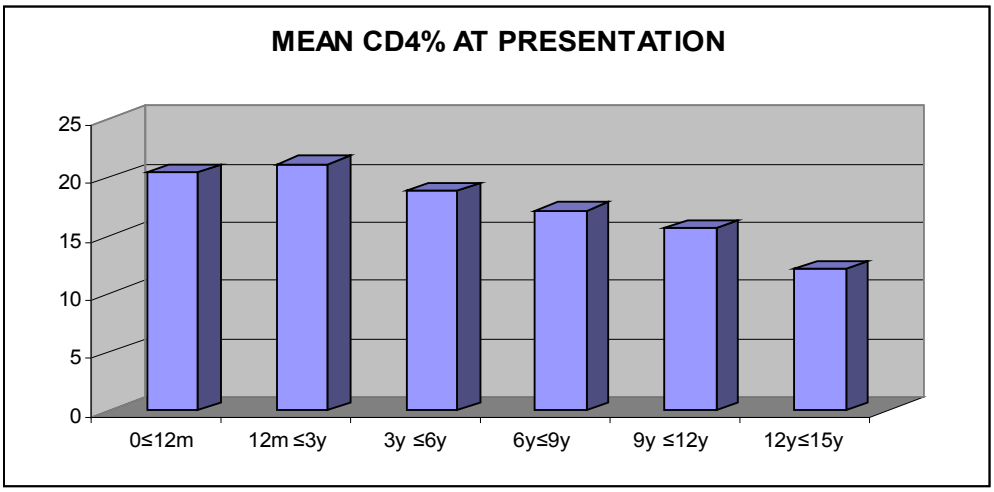
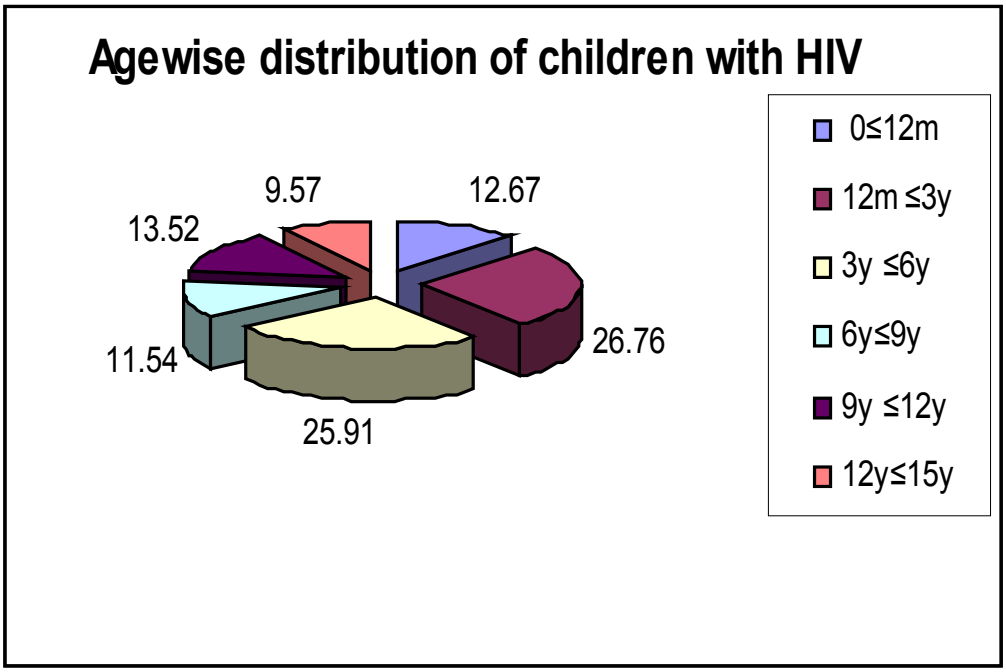
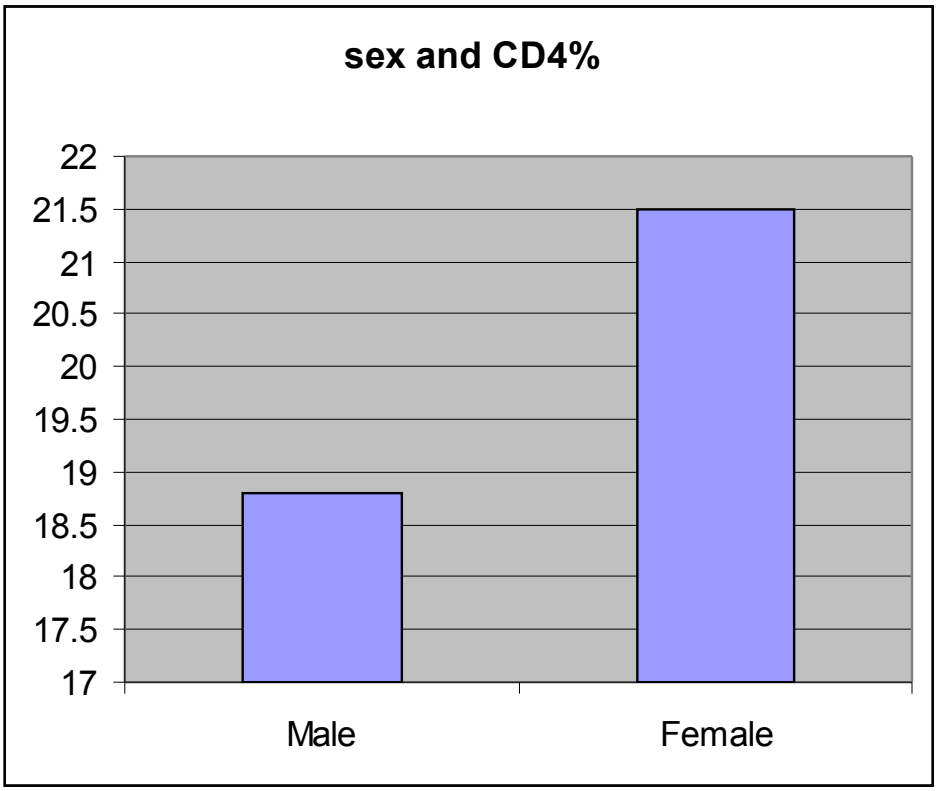
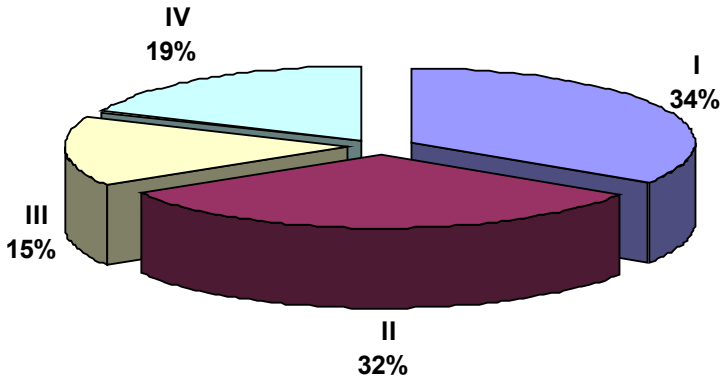

Sexwise distribution of children with HIV
Female
44%
Male
56%


MEAN CD4% AT PRESENTATION
25
20
15
10
5
0
0≤12m
12m ≤3y
3y ≤6y
6y≤9y
9y ≤12y
12y≤15y

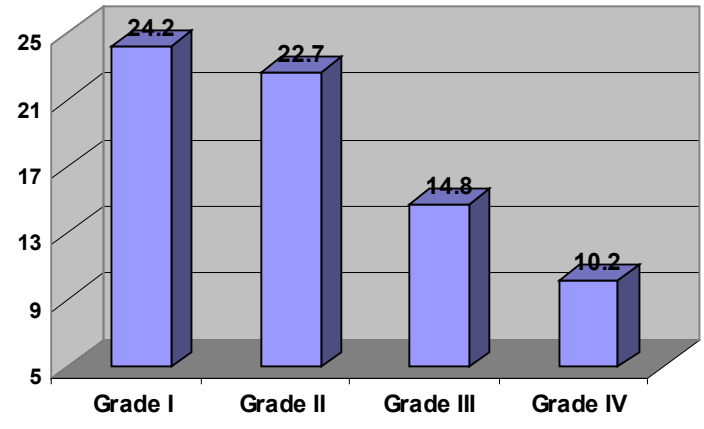

Agewise distribution of children with HIV
9.57
12.67
13.52
26.76
11.54
25.91
0≤12m
12m ≤3y
3y ≤6y
6y≤9y
9y ≤12y
12y≤15y

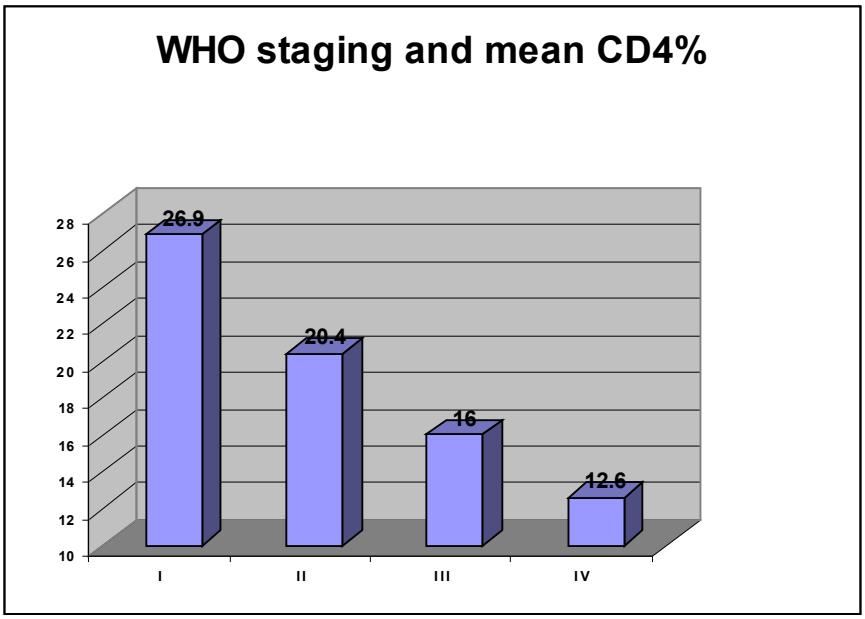

sex and CD4%
22
21.5
21
20.5
20
19.5
19
18.5
18
17.5
17
Male
Female

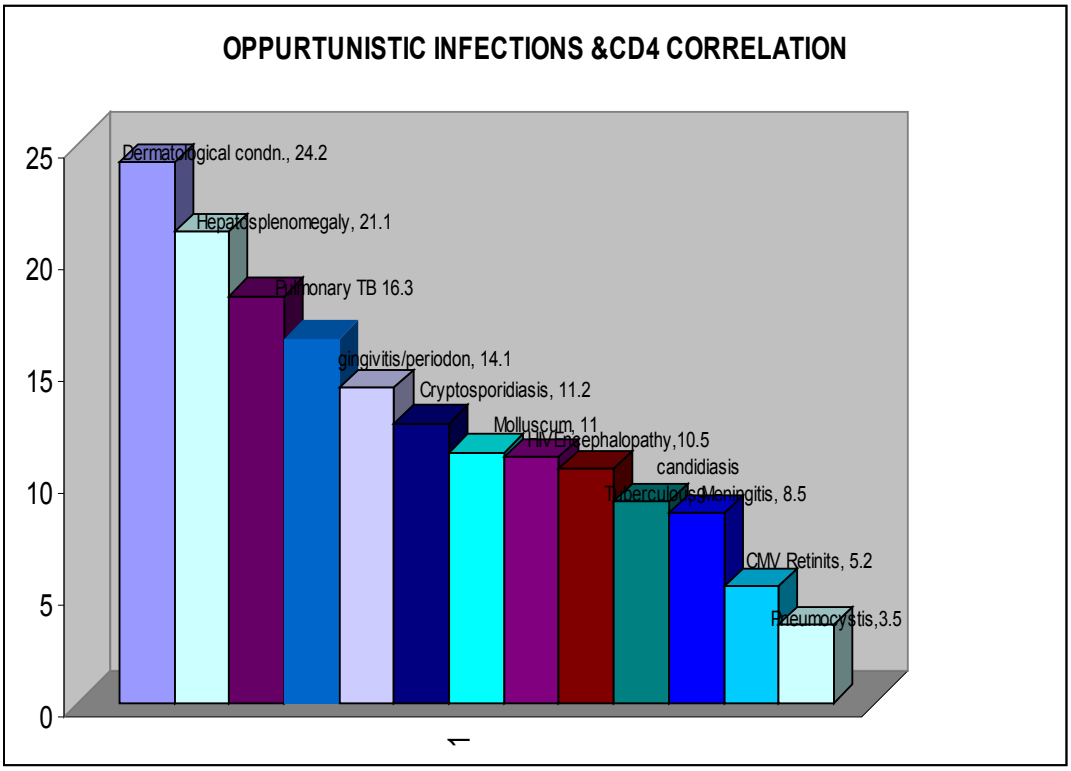
WHO STAGING

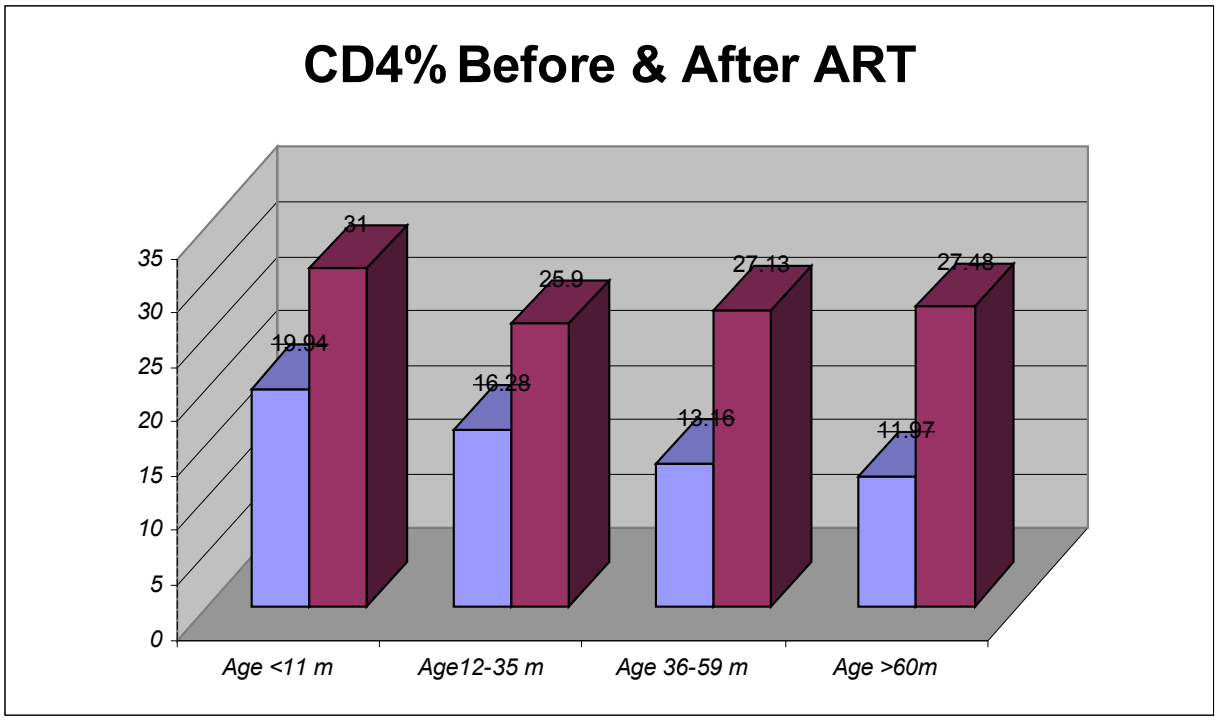


severity of PEM and CD4%




WHO staging and mean CD4%
28
26
24
22
20
18
16
14
12
10
26.9
20.4
16
12.6
I
II
III
IV


OPPURTUNISTIC INFECTIONS &CD4 CORRELATION
25
20
15
10
5
0
Dermatological condn., 24.2
Hepatosplenomegaly, 21.1
Pulmonary TB 16.3
gingivitis/periodon, 14.1
Cryptosporidiasis, 11.2
Molluscum, 11
HIV Encephalopathy,10.5
candidiasis
Tuberculosis
Meningitis, 8.5
CMV Retinits, 5.2
Pneumocystis,3.5
1


CD4% Before & After ART
35
30
25
20
15
10
5
0
19.94
31
16.28
25.9
13.16
27.13
11.97
27.48
Age <11 m
Age12-35 m
Age 36-59 m
Age >60m

ANNEXURE

WHO Clinical Staging of HIV for Infants and Children with Confirmed HIV Infection

Clinical Stage 1

Asymptomatic

Persistent generalized lymphadenopathy

Clinical Stage 2

Unexplained persistent hepatosplenomegaly

Papular pruritic eruptions

Extensive wart virus infection

Extensive molluscum contagiosum

Recurrent oral ulcerations

Unexplained persistent parotid enlargement

Lineal gingival erythema

Herpes zoster

Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)

Fungal nail infections

Clinical Stage 3

Unexplainedi moderate malnutrition not adequately responding to standard therapy

Unexplained persistent diarrhoea (14 days or more)

Unexplained persistent fever (above 37.5oC intermittent or constant, for longer than one month)

Persistent oral candidiasis(after 6-8 weeks of age)

Oral hairy leukoplakia

Acute necrotizing ulcerative gingivitis/periodontitis

Lymph node TB

Pulmonary TB

Severe recurrent bacterial pneumonia

Symptomatic lymphoid interstitial pneumonitis

Chronic HIV-associated lung disease including bronchiectasis

Unexplained anemia(<8gm/dl, neutropenia(<0.5×10^9/l,thrombocytopenia(50×10^9/l)

Clinical Stage 4

Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy

Pneumocystis pneumonia

Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)

Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)

Extrapulmonary TB

Kaposi sarcoma

Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)

Central nervous system toxoplasmosis (after one month of life)

HIV encephalopathy

Cytomegalovirus infection: retinitis or CMV infection affecting another organ, with onset at age over 1 month.

Extrapulmonary cryptococcosis (including meningitis)

Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis)

Chronic cryptosporidiosis

Chronic isosporiasis

Disseminated non-tuberculous mycobacteria infection

Cerebral or B cell non-Hodgkin lymphoma

Progressive multifocal leukoencephalopathy

Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy